Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference KOTO-19/PCT	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/JP2004/008678	International filing date *(day/month/year)* 15.06.2004	Priority date *(day/month/year)* 27.06.2003
International Patent Classification (IPC) or national classification and IPC		

Applicant

KOTOBUKI PHARMACEUTICAL CO., LTD.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:

      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

Form PCT/IPEA/409 (cover sheet) (January 2004)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/008678

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the claims:

nos. _____ as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* _____ received by this Authority on _____

nos.* _____ received by this Authority on _____

☐ the drawings:

sheets _____ as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/008678

Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 8

because:

☒ the said international application, or the said claims Nos. 8
relate to the following subject matter which does not require an international preliminary examination (*specify*):

The invention set forth in claim 8 pertains to a method for the treatment of the human body by means of therapy, and thus relates to a subject matter for which it is not necessary to carry out an international preliminary examination (PCT Article 34(4)(a)(i) and PCT Rule 67.1(iv)).

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 8

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
☐ has not been furnished
☐ does not comply with the standard

the computer readable form
☐ has not been furnished
☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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PCT/JP2004/008678

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-7	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-7	NO
Industrial applicability (IA)	Claims	1-7	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The written opinion was drafted based on the disclosures in documents 1 to 3, which are cited in the international search report, and documents 4 and 5, which are newly cited in the present written opinion.

Document 1: WO 02/058732 A2 (Schering Corp.)

Document 2: JP 8-505141 A (Schering Corp.)

Document 3: WO 02/066464 A1 (Kotobuki Pharmaceutical Co., Ltd.)

Document 4: M. HEEK et al., Br. J. Pharmacol., 2000, 129, pp. 1748 to 1754

Document 5: ZETIA: Prescribing Information [Online]. MERCK/Schering-Plough Pharmaceuticals, 2001, 2002 [Retrieved on 09 May 2005], Retrieved from the internet: <URL: http://www.drugs.com/PDR/zetia_tablets.html> (Zetia tablets professional drug information, published in March 2003, REV 01), <URL: http://www.zetia.com/zetia/shared/documents/zetia_pi.pdf> (published in March 2005, REV 07)

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Claims 1 to 7

Document 1 (claims and examples) and document 2 (claims and examples) indicate that the serum cholesterol-lowering action and the therapeutic and/or prophylactic action in relation to atherosclerosis were augmented by configuring so that the active component comprises a combination of a β-lactam compound that serves as a cholesterol-lowering agent and a fibrate compound or other such cholesterol biosynthesis inhibitor. Therein, a comparison of the inventions that are set forth in claims 1 to 7 and the inventions that are disclosed in documents 1 and 2 shows that the former inventions differ from the latter inventions in the light of the specific compounds that are employed therein.

However, the fact that β-lactam compounds exhibit a cholesterol absorption-inhibiting action is well known to a person skilled in the art, as disclosed in documents 1 to 3, and the specific compounds in question are also well known, as disclosed in document 3; therefore, it cannot be said to have required significant creativity for a person skilled in the art to conceive of attempting to employ the specific compounds that are disclosed in document 3 in the place of the compounds that are disclosed in documents 1 and 2.

Meanwhile, in the written response dated 21 December 2004, the applicant asserts that:

(i) whereas the β-lactam compounds that are disclosed in document 3 directly inhibit the absorption of cholesterol in the small intestine without being absorbed in the intestines, the compounds disclosed in documents 1 and 2 are known to inhibit the absorption of cholesterol as a

result of being absorbed by the intestines, metabolized, transferred into the blood as an active material and then secreted into the digestive tract within the bile, as disclosed in documents 3 and 4, and that therefore, based on the different *in vivo* behaviors of the compounds in question it would be natural to presume that the *in vivo* pharmacological behaviors thereof will also differ when combined with other medicaments; and

(ii) although the examples in the description of the present application indicate that it is possible to achieve a synergistic effect by using combinations of medicaments and document 2 also indicates that a combination of a β-lactam compound and lovastatin exhibited a synergistic effect, document 5 suggests that the effects in question are thought to result from a pharmacodynamic interaction that causes or worsens side effects, and the compounds that are disclosed in document 1 are considered to exhibit effects similar to those of the compounds that are disclosed in document 2 due to the fact that said compounds have chemical structures similar to those of the compounds disclosed in document 2; therefore, the present inventions, which employ the compounds that are disclosed in document 3, exhibit superior effects in comparison to the inventions that are disclosed in documents 1 and 2.

However, the fact that the *in vivo* environment including the *in vivo* behavior of the drug will have a significant effect upon the pharmacological expression of drugs that express therapeutic effects via absorption and metabolism *in vivo* is well known to a person skilled in

the art; therefore, it is common practice for a person skilled in the art to attempt to substitute such medicaments with medicaments that exhibit a similar therapeutic effect without having to be absorbed or metabolized, and the same is true with regards to attempting to substitute the compounds that are disclosed in documents 1 and 2, which exhibit the therapeutic effect of inhibiting the absorption of cholesterol in the small intestine, with the compounds that are disclosed in document 3.

In addition, with regards to the synergistic effects of the compounds, the examples set forth in the description of the present application and the examples disclosed in documents 1 to 3 employ different testing methods; therefore, the invention that is set forth in the present application cannot be considered to exhibit an especially superior action in comparison to the inventions that are disclosed in documents 1 to 3; likewise, with regards to the side effects, documents 3 and 4 indicate that the compounds that are disclosed in documents 1 and 2 and the compounds that are disclosed in document 3 behave differently *in vivo*; therefore, it can be considered to be natural for a person skilled in the art to attempt to confirm whether this is the case.

As a result, the abovementioned assertions in the written response are not applicable, and thus the inventions that are set forth in claims 1 to 7 do not involve an inventive step in the light of the disclosures of documents 1 to 5.